UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/666,778 | 09/18/2003 | Alain Goossens | 2676-6085US | 8721 |

24247 7590 02/26/2008

TRASK BRITT
P.O. BOX 2550
SALT LAKE CITY, UT 84110

| EXAMINER | |
|---|---|
| KALLIS, RUSSELL | |
| ART UNIT | PAPER NUMBER |
| 1638 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 02/26/2008 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTOMail@traskbritt.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/666,778 | GOOSSENS ET AL. | |
| | Examiner | Art Unit | |
| | Russell Kallis | 1638 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-13 and 15-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 15-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The finality of the office action filed 7/31/2007 is withdrawn in view of the following action.

Claims 1-13 and 15-21 are pending and examined.

Rejection of Claim 21 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of Applicants' amendments.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The remarks submitted with the pre-appeal request are considered moot in view of the withdrawl of finality.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Jasinski M. *et al.* Bulletin de la Societe Royale des Sciences de Leige; 1999, Vol. 68, No. 5-6 p. 323; in light of Jasinski M. *et al.* The Plant Cell, May 2001; Vol. 13, pp. 1095-1107 and attached sequence report.

The claim is drawn to an isolated polynucleotide sequence comprising a sequence having at least 91% sequence identity to the polypeptide sequence of SEQ ID NO: 2.

Jasinski teaches molecular cloning and characterization of a plasma membrane ABC-type transporter in Nicotiana Plumbaginifolia with an open reading frame of 4311 nucleotides that was induced by sclareol, a plant diterpene (i.e. a secondary metabolite) found on the leaf surface of *Nicotiana* species.

Jasinski (The Plant Cell) and the attached sequence report provides evidence that NpABC1 has at least 91% sequence identity to SEQ ID NO: 2; and thus the reference has all the limitations of Claim 15.

### *Claim Rejections - 35 USC § 103*

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 10-13, and 16-19 are rejected under 35 U.S.C. 103(a) as obvious over Muhitch, M. *et al.* Plant Science, 2000, Vol. 157, pp. 201-207 in view of itself.

The claims are broadly drawn to processes of enhancing secretion of an unspecified secondary metabolite from an unspecified plant or plant cell transformed with a vector comprising a gene encoding an ABC-transporter and selecting thereby; and plants and plant cells thereof.

Muhitch teaches selection of tobacco transformed with the yeast PDR5 multi-drug transporter (an ABC transporter) for tobacco resistant to trichothecene 4,15-diacetoxyscirpenol (DAS) a mycotoxin secondary metabolite produced by fungal species; (see abstract and the discussion especially page 206 column 1 line 14 to column 2 end of section).

It would have been obvious to one of ordinary skill to further characterize the assumptions about the *in planta* activity of the transporter transgene for research purposes by determining the mode of action of the transgene product; i.e. secretion of the fungal mycotoxin by the ABC transporter (see page 206 column 1 lines 18-23). One of ordinary skill would been motivated by the teachings of Muhitch to further characterize the mode of action and would have a reasonable expectation of success given the success of Muhitch in transforming tobacco with the yeast PDR5 encoding transporter gene and selecting for mycoresistant plants and plant cells.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13 and 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rea *et al.* WO 98/21938.

The claims are broadly drawn to processes of inducing or enhancing secretion or production of an unspecified secondary metabolite from an unspecified plant or plant cell transformed with a vector comprising a gene encoding an ABC-transporter and selecting thereby; and plants and plant cells thereof.

WO 98/21938 (Rea) teaches GS-X an ABC transporter that is active in storing pigment (i.e. a secondary metabolite) by transport into Maize vacuoles; a method for increasing pigment transport into plant vacuoles by transformation with GS-X (see pages 1-6, 87-91 especially page 88 first full paragraph to page 89 end of paragraph and claims 24-25); and the efficacy of medicarpin (an alkaloid) as a substrate for the vacuolar GS-X pump, an ABC transporter, (on page 87 lines 3-19 and claim 24).

It would have been obvious to one of ordinary skill in the art to transform a plant with the GS-X ABC transporter of Rea and select for either increased production or secretion of either a medicarpin (alkaloid) or anthocyanin in the vacuoles of either a whole plant or plant cells. One of ordinary skill would have been motivated by the teachings of Rea that both an alkaloid and a pigment could be targeted to a plant vacuole for increased transport using a plant GS-X ABC transporter, would have a reasonable expectation of success in screening for increases in either secretion or production into the vacuole of either anthocyanin or medicarpin given the teachings and success of Rea as presented supra.

Claims 1-13 and 15-19 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Theodoulou F. Biochemica et Biophysica Acta; 2000, 1465, pp. 79-103 in view of Dudler R. *et al.* Journal of Biological Chemistry; 25 March 1992, Vol. 267, No. 9 pp. 5582-5888 in further view of Sidler M. *et al.* The Plant Cell, October 1998; Vol. 10, 1623-1636. This rejection is maintained for the reasons of record set forth in the Official action mailed 7/31/2007. Applicant's arguments filed 9/28/2007 have been considered but are not deemed persuasive.

The claims are broadly drawn to processes of enhancing secretion of an unspecified secondary metabolite from an unspecified plant or plant cell transformed with a vector comprising a gene encoding an ABC-transporter and selecting thereby; and plants and plant cells thereof.

Theodoulou teaches ABC transporter genes from plants that have strong similarity to MDR proteins from other species and suggests a role of the plant homologues in the secretion or sequestering of *vinca* alkaloid and the alkaloid taxol and suggests a strategy for screening transformed plants and plant cells for determining the specific transport function (section 5.2 page 86).

Dudler teaches an MDR like gene (*AtPGP1*) from Arabidopsis, having nucleotide binding sites (i.e. walker A and B) and transmembrane domains in Figure 6a; and suggests testing to identify substrates (See Abstract and column 1 page 5888 lines 4-7 and 40-53).

Sidler teaches transformation of *Arabidopsis* with the *AtPGP1* gene of Dudler (an ABC transporter having Walker A and B motifs that is recognized in the art as a nucleotide binding fold) where over expression (in the plasmalemma) resulted in an increase in hypocotyls length (see Abstract; page 1629 column 2 1st paragraph of discussion lines 1-8; and page 1631 column 1 line 28 or 2nd full paragraph); and strongly suggested a transport process (lines 8-9 Abstract).

It would have been obvious at the time of Applicant's filing to take any ABC transporter gene that encoded a protein that had similar structural motifs to the human MRD ABC transporter and test for induced or enhanced production or secretion of any secondary metabolite such as the vinca alkaloid or taxol to determine the function of the

plant MDR homologue. One of ordinary skill in the art would have been motivated by the teaching of Theodoulou and by Sidler, that taxol, and other plant secondary metabolites are substrates of, or bind to MDR ABC transporter proteins, and would be useful in the art of bioengineering 'secondary product' production and secretion in plants or plant cells that produce taxol, *vinca* alkaloid or other pant secondary compounds; and have had a reasonable expectation of success given the success of Sidler, and that transgenic strategies for evaluating the specific function of plant ABC transporter genes were within the reach of one of ordinary skill and available in the art, and that non-plant alkaloid transporters and methods of transforming plants and maintaining plant cell cultures, and selecting for the production of secondary metabolites and screening for vacuolar transport or secretion are obvious method steps given the teachings of Theodoulou as discussed supra; wherein selecting for increases in secretion or production relative to a control are obvious design steps within the practice of one of ordinary skill.

Applicant asserts that the references do not teach the exact function of the ABC transporter *AtPGP1* and thus the claim limitation is not taught in the prior art (response page 7 lines 3-7). It would be remiss upon the examiner if it was not pointed out that the claims are not drawn to any specific or exact activity or function other than the broadly claimed transport of an unspecified secondary metabolite. In addition, the method does not require knowledge of the exact function or metabolite specificity, but rather is permissive for the discovery of that activity during the selection step. Further, the prior art (Sidler) suggests that AtPGP1 transports a regulator involved in light dependent hypocotyl elongation, and speculates that it may be a peptide. However one must also consider what is well known in the art, that hypocotyl elongation is a response to auxin,

which is a secondary metabolite. Moreover, from Applicant's specification on page 11, AtPGP1 is listed as an embodiment of the invention;

> "An MDR-like gene (atpgp1) has also been identified in A. thaliana, which encodes a putative P-glycoprotein homolog. This atpgp1 gene was found to share significant sequence homology and structural organization with human MDR genes. Other MDR homologues have been found in potato and barley. Genes encoding ABC-transporters of the present invention which may be operably linked with a promoter for expression in a plant species may be derived from a chromosomal gene, cDNA, a synthetic gene, or combinations thereof.";

and thus contrary to Applicant's assertions one of ordinary skill would have a reasonable expectation of success.

Applicant points to Claims 1, 7 and 16 as reciting the limitations "selecting transformed plant cells having an induced or enhanced production or secretion of at least one secondary metabolite" and "selecting transformed plant cells exhibiting enhanced transport of said at least one secondary metabolite into a vacuole" as examples of limitations that are not met in the references cited (response page 7). Clearly, the references direct one of ordinary skill to characterize the ABC transporters for the type of secondary metabolite transported and vacuolar transport using a transgenic plant approach (see Theodoulou page 84 section 4. the emergence of plant ABC transporters in columns 1-2, especially lines 5-15 of column 2; and all of section 5 on page 86, especially column 2 lines 12-24; and all of section 6); and thus one of ordinary skill in the art is directed to transform plants with ABC transporter genes and select for induced or enhanced activity.

Applicants assertion that selection was not based upon either production of the gene product of the AtPGP1 gene or its' location of transport is inconsistent with the teachings of the reference (response page 7). Sidler teaches that plants overexpressing the

AtPGP1 ABC transporter grew longer hypocotyls when compared to antisense and wild type plants and this was correlated with increased expression of the AtPGP1 gene product as made evident by immunoblotting of microsomal membrane fractions (on page 1624 column 1 lines 18-31). Moreover, one of ordinary skill in the art would have appreciated that the hypocotyl elongation observed in the transgenic plants was the result of increased transport into the hypocotyl cells and would have considered other alternatives than those presented in the reference such as the well known activity of auxin in hypocotyl elongation. Further, Applicant's IDS teaches the state of the prior art with reference to WO 98/21938 (Rea) that teaches GS-X an ABC transporter that is active in storing pigment (i.e. a secondary metabolite) by transport into Maize vacuoles and a teaches a method for increasing pigment transport into plant vacuoles by transformation with GS-X (see pages 1-6 and 87-89; and claim 25). Therefore, the state of the art was actively involved in isolating, characterizing i.e. selecting for expression above wild type including vacuolar accumulation, and transforming said ABC transporter genes into plants. Applicant's remarks concerning improper hindsight are not well founded and are addressed supra.

Applicant's assertion that any metabolite transported by AtPGP1 is a primary metabolite because it is involved in survival and hence is a primary metabolite is based upon Applicant's faulty interpretation of the results of antisense experiments where a complete knockout of gene expression was not observed. This reasoning is faulty because it is well known in the art that it is rare to have a complete knock out of gene expression using antisense. Further, Applicant's IDS teaches the state of the prior art with reference to WO 98/21938 (Rea) that teaches GS-X an ABC transporter that is active in storing

pigment (i.e. a secondary metabolite) by transport into Maize vacuoles and a teaches a method for increasing pigment transport into plant vacuoles by transformation with GS-X (see pages 1-6 and 87-89; and claim 25). Furthermore, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that the references do not teach the limitations discussed supra, the test for obviousness is not that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Applicant asserts that the role suggested in the art for P-gp is clearly distinct from the claim limitation of "capable of enhancing or stimulating the production or secretion of that [secondary metabolite] compound" (response page 8). However, the claims are not limited only to 'enhancing or stimulating', but rather recite inducing (claim 1). Nonetheless, the increased expression of AtPGP1 and the increase in hypocotyls elongation observed in Sidler as stated supra, combined with the knowledge of the structure of AtPGP1 as an ABC transporter, it would be well understood by one of

ordinary skill that the increased expression of AtPGP1 would result in the increased transport of a secondary metabolite.

In the Declaration of Alain Goossens, most of the examples submitted do not fall with in the scope of the claims because they are not transporters and do not possess the Walker A and B motif as well as the nucleotide binding fold as recited in the claims. Moreover, contrary to Applicant's assertion in the declaration and remarks thereof that their results were unexpected, in adition to the prior art cited supra, the prior art does provide several other examples; the first show increases in nicotine levels in *Nicotiana rustica* cells transformed with ornithine decarboxylase (Hamill, J., *et al.* Plant Molecular Biology, Vol. 15, 1990 pp. 27-38) see Abstract and page 36 figure 7 and surrounding discussion)

A second example of transgenic *Nicotiana* cells accumulating a secondary metabolite in both the cells and medium is provided by (Hallard D. et al. Plant Cell Reports, 1997, Vol. 17; pp. 50-54) where strictisidine, not normally synthesized in *Nicotiana*, accumulated in the medium of cells transformed with trytophan decarboxylase and strictosidine synthase (see abstract and discussion on pages 52-53 and figure 3).

A third example is found in Muhitch M. *et al.* Plant Science, 2000, Vol. 157, pp. 201-207 see abstract and the discussion especially page 206 column 1; where tobacco transformed with the yeast PDR5 multi-drug ABC transporter produced tobacco resistant to trichothecene 4,15-diacetoxyscirpenol (DAS) a mycotoxin secondary metabolite produced by fungal species.

A fourth example is provided by Sato F. *et al.* PNAS January 2, 2001 vol. 98, no. 1 pp. 367-372. Sato teaches both putrescine N-methyltransferase (PMT) overexpression

in *N. sylvestris* cells yielded transformed cells having higher nicotine content when compared to controls and heterologous expression of S-methyltransferase in *E. Californica* yielded transformed cells that produced accumulation of benzylisoquinoline alkaloids relative to control (see abstract).

Applicant's conclusions on page 8 of the response, that the possibility of a gene being involved in the synthesis 'and/or' compartmentation of a secondary metabolite does not translate into a reasonable expectation of success that the gene is involved in the production or secretion of a secondary metabolite. Clearly, Applicant is comparing apples and oranges because the claims are not drawn to only to increased synthesis, but rather are drawn to induced or enhanced production or secretion; or enhanced transport. Moreover, those portions of the declaration showing unexpected results have already been considered, they are part of the original specification and have deemed allowable; see objected claims 20-21. The declaration was not given any additional weight because it provided no new evidence for the claimed genus of ABC transporters. Applicant's statements that the Examiner has provided no evidence other than to indicate that it was considered irrelevant is a gross misrepresentation of the Examiner's remarks (also see art cited supra). Clearly an analysis was performed and the declaration was evaluated. Moreover, Applicant has failed to respond to the Examiner's arguments per *in re Lindner*, and is repeated below.

Applicant has demonstrated an induced or enhanced production or secretion of only a nicotine based alkaloid in tobacco transformed with SEQ ID NO: 1. In contrast, the method claims are broadly drawn to a multitude of ABC sequences from a multitude of sources having no specific secondary metabolite specificity, including animal, fungal

and plant genes encoding ABC transporters; see *In re Lindner*, 173 USPQ 356 (CCPA 1972) and *In re Grasselli*, 218 USPQ 769 (Fed. Cir. 1983) which teach that the evidence of nonobviousness should be commensurate with the scope of the claims.

No claim is allowed.

Claims 20-21 are objected to as being dependent upon rejected base claim 15, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (571) 272-0798. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Russell Kallis/
Primary Examiner of Art Unit 1638
January 31, 2008